Headspace Analysis of Organic Volatile Impurities by USP <467> Using the DB-624 and the HP-Fast GC Residual Solvent Column

Application

Drug Manufacturing/QA/QC, Drug Testing, and Production-QA/QC

Authors

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Abstract

The United States Pharmacopeia (USP) <467> specifies the gas chromatographic conditions, injection technique, and column type and dimensions for the analysis of organic volatile impurities (OVIs) in bulk pharmaceuticals and excipients. This USP method also specifies the maximum permissible levels of five solvents in pharmaceutical products. In this application, experimental conditions are described detailing the headspace analysis of these solvents using the Agilent 6890 GC and the standard dimension 3.0 µm DB-624 (G-43 equivalent phase) column. The work was extended to include the same analysis using the HP-Fast GC Residual Solvent column to reduce the separation time by almost a factor of three without loss of component resolution. Good linearity and precision are obtained over the concentration range of interest for both columns.

Introduction

USP <467> [1, 2] documents the methodologies for evaluating organic volatile impurities (OVI) present in pharmaceutical formulations and excipients.

This USP method details the use of three sample introduction techniques including direct (splitless) injection, described in Method components I and V; dynamic headspace (purge and trap) injection, described in Method components II and III; and static headspace, described in Method component IV. The USP Method specifies the analysis of five solvents and the maximum allowable concentrations. The solvents of interest include:

Methylene chloride	100 ppm
Benzene	100 ppm
Trichloroethylene	100 ppm
1,4-Dioxane	100 ppm
Chloroform	50 ppm

In the Gudat and Sievert [3] evaluation of static headspace and direct sample introduction techniques for these solvents, the authors concluded that even though both methods were acceptable for the analysis, the static headspace method was preferred because of increased sensitivity for chloroform. In addition, with the static headspace method, the GC system was not as easily contaminated, which reduced the need for routine maintenance [4].

Firor, et al. [5], showed that good precision and linearity were obtained for the five solvents when using short headspace heating times and vigorous agitation. Chang, et al. [6], and Brillante, et al. [7], showed that the optimized headspace conditions worked well for the efficient transfer of the solvents but selected the HP-INNOWax capillary

column to do the separation. Although the stationary phase was not equivalent to the G-43 phase specified in the method (DB-624 column), the analysis time was short and the data demonstrated good precision and linearity.

Experimental

A standard stock solution of the five solvents was prepared as previously described [6]. One half gram (0.5 grams) of chloroform and one gram each of the other solvents was dissolved in 100 mL of methanol. The stock solution was stored in a refrigerator until needed. A series of working standards was prepared daily by diluting the equivalent of 2 µL to 200 µL of stock solution to 100 mL with organic-free 18 megohm water. For the GC analysis, 5 mL of each working standard was placed in a headspace vial containing 1.0 ±0.1 gram of anhydrous sodium sulfate and sealed immediately. The samples were mixed with a vortex mixer to dissolve any insolubles.

The Agilent 7694 headspace sampler equipped with a Silcosteel® transfer line was used as the injection device. The GC analysis was done using an Agilent 6890 GC. All headspace and GC operating conditions are listed in Table 1. Both the standard DB-624 column and a new HP-Fast GC Residual Solvent column designed for rapid solvent analysis were evaluated for this analysis.

Results and Discussion

The objectives of this work were to first verify the suitability of the standard DB-624 column that is equivalent to the G-43 phase for the analysis of the five solvents at the concentrations specified by USP <467>. Second, we wanted to evaluate the suitability of an HP-Fast GC Residual Solvent column for the analysis of these solvents to reduce the GC analysis time to less than 10 minutes.

Figure 1 shows a typical chromatogram of the OVI components obtained using the chromatographic conditions and the standard G-43 column specified in the USP method. The sample analysis time including the headspace, GC analysis, and oven cooldown is complete in about 45 minutes. The oven ramp is slow at the beginning when the solvent peaks are eluting from the column then is ramped up quickly to remove less volatile components and clean the column before the next injection.

Table 1. Headspace and GC Operating Conditions

Headspace conditions	
Carrier gas pressure:	3.5 psi
Oven temp:	85 °C
Loop temp:	95 °C
Transfer line temp:	110 °C
Vial pressure:	10 psi
Vial equilibration time:	10 min
Pressurization time:	0.2 min
Loop fill time:	0.15 min
Loop equilibration time:	0.05 min
Injection time:	1.00 min
GC Conditions using the standard G-43 (DB-624) column	
GC:	6890
Column:	DB-624, 30 m × 0.53 mm × 3.0 µm (part no. 125-1334)
Carrier:	Helium, 35 cm/min, constant flow
Oven:	40 °C (5 min) to 90 °C at 2 °C/min 90 °C to 250 °C at 30 °C/min
Injection:	Headspace, 180 °C, split 7/1
Detector:	FID, 260 °C
GC Conditions using the Fast G-43 (HP-Fast GC Residual Solvent) column	
GC:	6890
Column:	HP-Fast GC Residual Solvent Column
(HP part no.	19095V-420)
Carrier:	Helium, 30 cm/min, constant flow
Oven:	40 °C (1.7 min) to 90 °C at 6 °C/min 90 °C to 250 °C at 30 °C/min
Injection:	Headspace, 180 °C, split 7/1
Detector:	FID, 260 °C

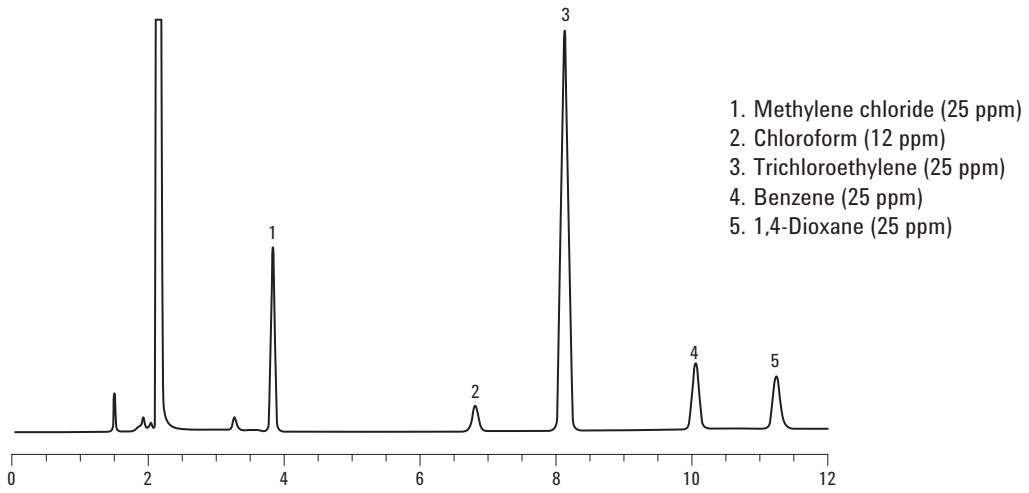

Figure 1. Headspace analysis of five organic volatile impurities using standard DB-624 column.

Table 2 shows a summary of the average area response and average %RSD calculated from the five replicate runs of each working standard for the concentration range shown. The average area responses for all the solvents were well below the range of 15% established by the USP method.

Table 2. Average Area Responses and Relative Standard Deviations

	2 ppm	10 ppm	25 ppm	50 ppm	100 ppm	200 ppm	Avg. % RSD
Methylene chloride	2.6	8.0	22.0	46.7	89.8	175.9	6.7
Chloroform	0.6	1.7	5.1	11.2	20.0	43.2	7.8
Benzene	8.8	30.0	88.9	201.9	392.1	805.4	5.4
Trichloroethylene	1.6	5.0	15.5	36.8	70.5	147.8	6.5
1,4-Dioxane	1.8	5.8	15.2	31.6	66.3	129.9	8.0

Figure 2 shows the calibration curve for chloroform. Linear response over the specified range was evidenced by the good correlation coefficient.

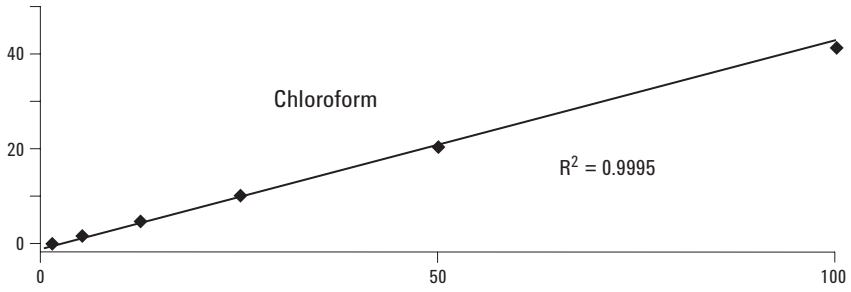

Figure 2. Calibration curve for chloroform.

Table 3 summarizes the calculated correlation coefficients and the estimated detection limits for the five solvents. The DB-624 column gave results within the allowable range set by the method.

Table 3. Correlation Coefficients and Calculated Minimum Detection Limits (S/N>3)

	Concentration range, ppm	Correlation coefficient	MDL ppm
Methylene chloride	2–200	0.9998	0.10
Chloroform	1–100	0.9995	0.70
Benzene	2–200	0.999	0.06
Trichloroethylene	2–200	0.9998	0.31
1,4-Dioxane	2–200	0.9990	0.32

To demonstrate the utility of the DB-624 column, a sample containing 22 different common solvents was prepared. In the resulting chromatogram (Figure 3), most of the solvents are resolved from one another and all solvents elute from the column within approximately 15 minutes. The second goal of this analysis was to reduce the analysis time by a factor of two so the GC separation could be completed in approximately the same time as the headspace introduction. To this end, a capillary column was designed specifically to complete the separation in less time while maintaining the desired resolution but with a stationary phase equivalent to the G-43 phase described in USP <467>.

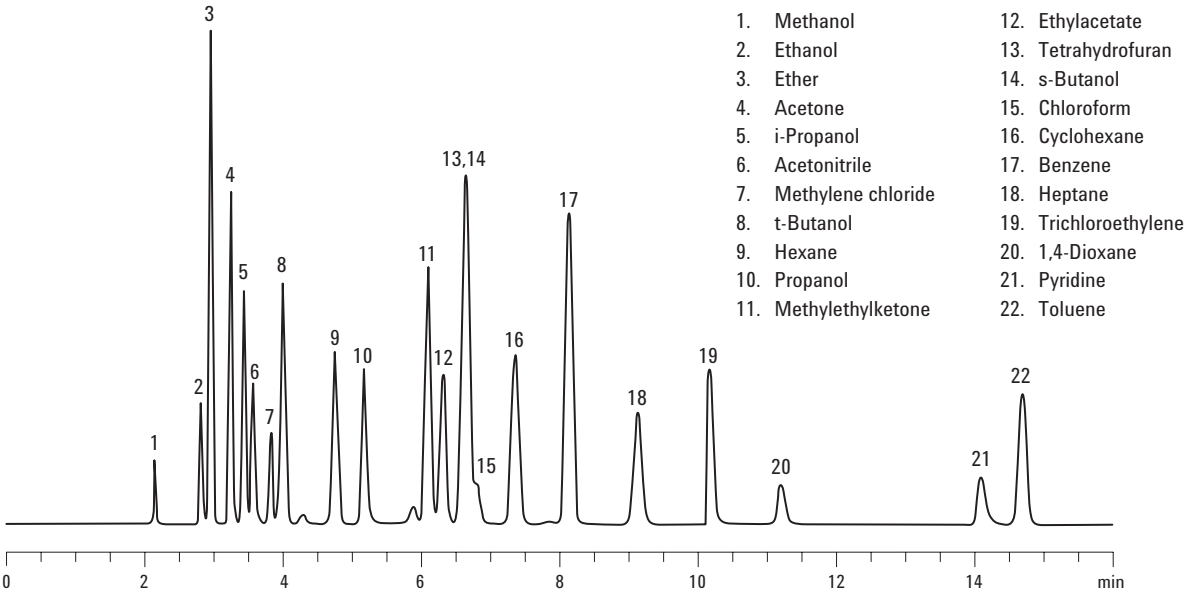

Figure 3. Solvent mixture on standard DB-624 column.

Figure 4 shows the analysis of the standard five solvents on the HP-Fast GC Residual Solvent column. The total analysis time including headspace, GC analysis, and oven cool-down is about 25 minutes. This is less than half the time required to complete the analysis on the standard (3.0 µm) DB-624 column. The reasons for the speed gain are the use of a faster temperature profile and a thinner stationary phase film thickness.

The performance of the HP-Fast GC Residual Solvent column was evaluated by correlation coefficients for the solvent calibration curves and peak area reproducibility. Calibration curves for each solvent were constructed using the same standard stock solutions and the same headspace conditions. The GC analysis was completed using the faster oven ramp detailed in Table 1.

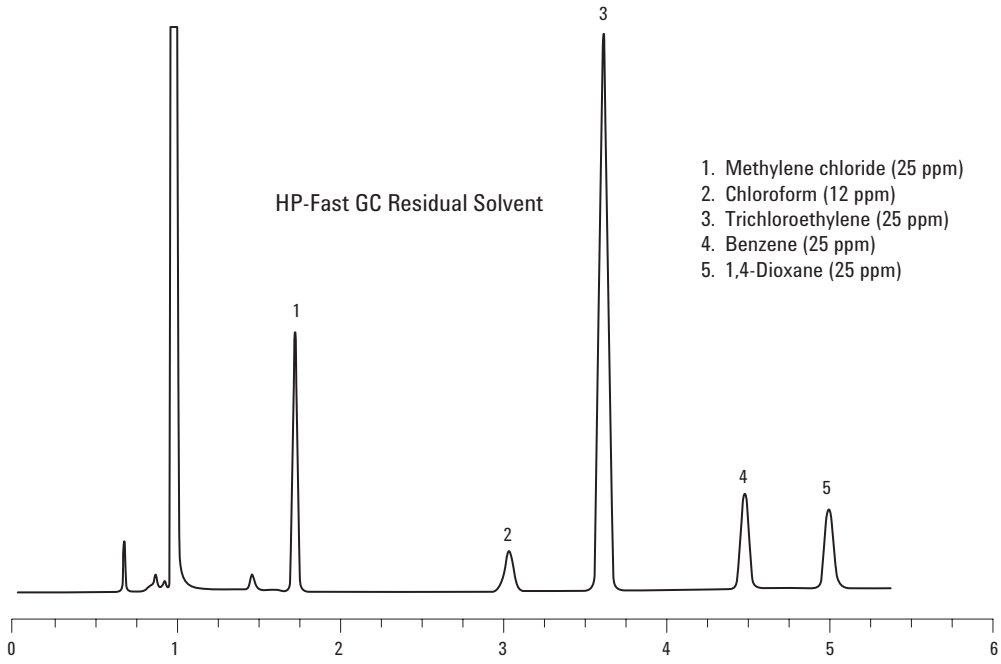

Figure 4. Headspace analysis of five organic volatile impurities using HP-Fast GC Residual Solvent column.

Table 4 shows a summary of the average area response %RSD calculated from the five replicate runs of each working standard for the concentration range shown on the HP-Fast GC Residual Solvent column. The average area responses for all five solvents on the HP-Fast GC Residual Solvent column were well below the range of 15% established by the USP method. In fact, the calculated values show slightly better reproducibility than the thicker film column.

Table 4 Average Area Responses and Relative Standard Deviations

	2 ppm	10 ppm	25 ppm	50 ppm	100 ppm	200 ppm	Avg. % RSD
Methylene chloride	5.4	19.8	54.0	106.3	201.4	387.1	3.2
Chloroform	1.4	4.3	10.9	20.9	39.1	77.4	4.1
Benzene	17.8	64.8	174.0	339.4	650.5	1295.2	4.6
Trichloroethylene	4.3	11.4	28.3	55.8	109.1	220.9	6.8
1,4-Dioxane	1.1	5.5	14.8	31.5	64.4	127.9	2.9

Figure 5 shows the calibration curve for chloroform as an example. Linear response over the specified range was evidenced by the good correlation coefficient. Here again the fast column gave slightly better linearity (higher correlation coefficients and estimated detection limits) than the standard column.

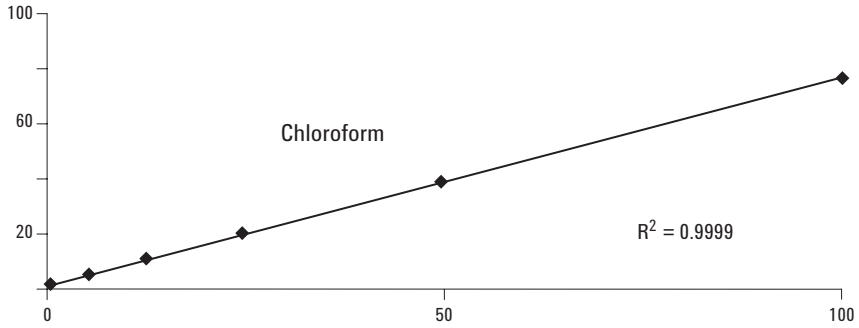

Figure 5. Calibration curve for chloroform on the HP-Fast GC Residual Solvent column.

Table 5 summarizes calculated correlation coefficients and an estimate of the detection limits for the solvents of interest.

Table 5. Correlation Coefficients and Calculated Minimum Detection Limits (S/N>3)

	Concentration range, ppm	Correlation coefficient	MDL ppm
Methylene chloride	2–200	0.9996	0.05
Chloroform	1–100	0.9999	0.28
Benzene	2–200	0.9999	0.04
Trichloroethylene	2–200	0.9999	0.18
1,4-Dioxane	2–200	0.9999	0.17

Another benefit of using the HP-Fast GC Residual Solvent column is that the peak widths are about one third of the peak width of the same component on the standard column. The reduced peak width resulted in the reduction of the minimum detectable amount of each one of the five solvents when the HP-Fast GC Residual Solvent column was used.

Figure 6 shows an example of a mixture of 22 different solvents on the HP-Fast GC Residual Solvent column. All separations were completed in approximately 6 minutes without loss of component resolution.

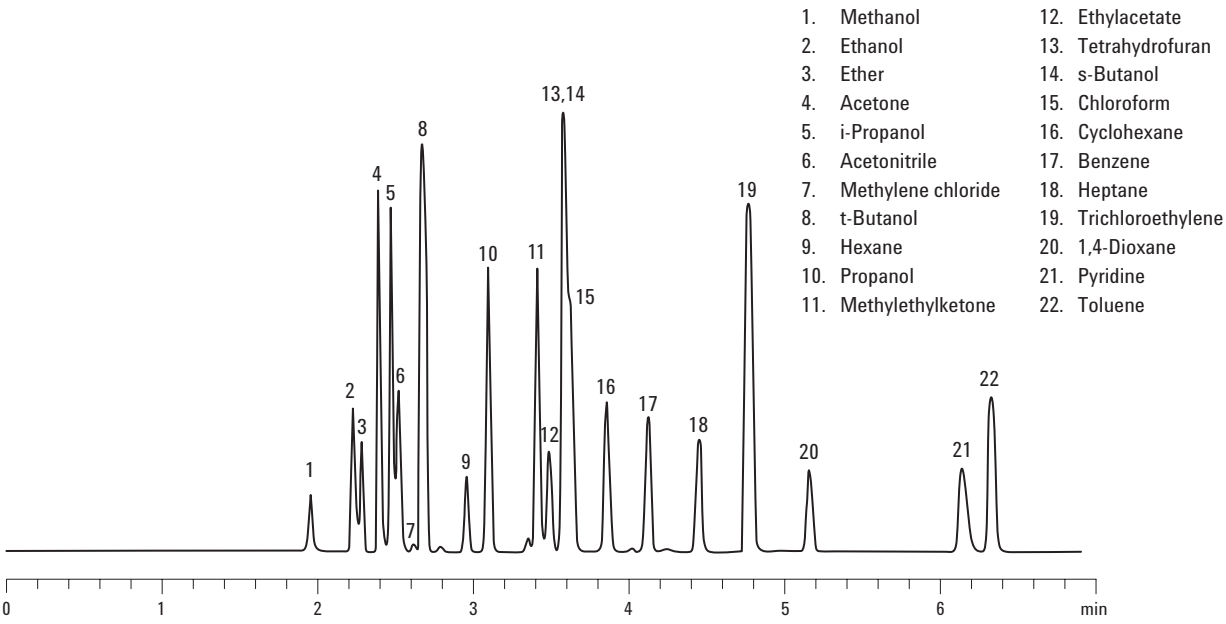

Figure 6. Solvent mixture on the HP-Fast GC Residual Solvent column.

Conclusion

The use of the standard DB-624 column with the Agilent 7694 headspace sampler and the Agilent 6890 GC resulted in the accurate and precise determination of the solvents specified in USP <467>. To reduce analysis times, the HP-Fast GC Residual Solvent column was developed. Using this column reduced analysis times by one half and actually provided better quantitation and lower detection limits.

References

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